



Published in final edited form as:

Exp Neurol. 2016 October ; 284(Pt B): 220–229. doi:10.1016/j.expneurol.2016.05.038.

Posttraumatic Stress Disorder: A Metabolic Disorder in Disguise?

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Abstract

Posttraumatic stress disorder (PTSD) is a heterogeneous psychiatric disorder that affects individuals exposed to trauma and is highly co-morbid with other adverse health outcomes, including cardiovascular disease and obesity. The unique pathophysiological feature of PTSD is the inability to inhibit fear responses, such that individuals suffering from PTSD re-experience traumatic memories and are unable to control psychophysiological responses to trauma-associated stimuli. However, underlying alterations in sympathetic nervous system activity, neuroendocrine systems, and metabolism associated with PTSD are similar to those present in traditional metabolic disorders, such as obesity and diabetes. The current review highlights existing clinical, translational, and preclinical data that support the notion that underneath the primary indication of impaired fear inhibition, PTSD is itself also a metabolic disorder and proposes altered function of inflammatory responses as a common underlying mechanism. The therapeutic implications of treating PTSD as a whole-body condition are significant, as targeting any underlying biological system whose activity is altered in both PTSD and metabolic disorders, (i.e. HPA axis, sympathetic nervous systems, inflammation) may elicit symptomatic relief in individuals suffering from these whole-body adverse outcomes.

Introduction

Post-traumatic stress disorder (PTSD) is a heterogeneous psychiatric disorder whose etiology stems from the occurrence of a psychological traumatic event (Kessler et al., 1995). Epidemiological studies indicate that while approximately 70% of the general population will experience a traumatic event in their lifetime, only 10-20% of those exposed to significant trauma will go on to develop PTSD symptoms. PTSD often presents symptoms

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across an array of different domains, including re-experiencing, avoidance, numbing, and hyperarousal (Kessler et al., 1995). The etiology and maintenance of PTSD is related to psychophysiological hyperarousal, an intermediate phenotype that is characterized by an exaggerated fear response (Glover et al., 2011; Jovanovic and Ressler, 2010) and deficits in fear extinction (Norrholm et al., 2015). Alterations in neuroendocrine, sympathetic, metabolic, inflammatory, neurotransmitter and neurobiological systems have all been described in those with PTSD [for review see (Michopoulos et al., 2015a)]. Importantly, PTSD is associated with an array of other adverse mental (e.g., major depression, substance and alcohol abuse, panic disorder, suicide) and physical health diseases and disorders (e.g., cardiovascular disease) (Boscarino, 2004; Jacobsen et al., 2001).

Obesity and metabolic disorders, including type 2 diabetes mellitus (T2DM), are also highly comorbid with PTSD (Rosenbaum et al., 2015). Guidelines for healthy, normal weight are currently based on body mass index (BMI) cut-offs recommended by the World Health Organization (FerroLuzzi et al., 1995). Metabolic syndrome is characterized by the presence of three of the following phenotypes: increased abdominal fat mass (large waist circumference, being overweight or obese), disrupted glucose regulation that often manifests as hyperglycemia (increased fasting plasma glucose), elevated blood pressure, increased levels of triglycerides and decreased levels of HDL cholesterol (National Cholesterol Education Program Expert Panel on Detection and Treatment of High Blood Cholesterol in, 2002). Obesity and metabolic disorder result in reduced sensitivity to the anorexigenic peptide leptin (secreted from adipose tissue) that results in hyperleptinemia and leptin resistance (Santoro et al., 2015). Hyperglycemia in metabolic disease, including T2DM, occurs in tandem with insulin resistance (Rosmond, 2005).

The high co-morbidity between obesity, metabolic disorders and PTSD suggest that underlying neuroendocrine and metabolic changes are present in PTSD that either increase the risk for systemic metabolic dysregulation or reflect a primary change in metabolism as a result of the traumatic experience. The current review will examine the convergence of PTSD and metabolic syndrome, and garner cause and effect sequelae from model animals. Furthermore, alterations in inflammatory signaling secondary to shifts in glucocorticoid receptor sensitivity will be entertained as a possible driving force behind both behavioral symptoms consistent with PTSD and co-occurring physiological manifestation of metabolic disease. Viewing PTSD as a psychiatric and metabolic condition has important treatment implications for eliciting symptomatic relief in individuals suffering from PTSD and its adverse sequelae.

The HPA Axis and Metabolic Alterations in PTSD

Alterations in both the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) are present in PTSD and have been extensively characterized (Michopoulos et al., 2015a). Glucocorticoids, cortisol in humans, are the main effectors of the stressor-activated HPA axis. Glucocorticoids bind to the glucocorticoid receptor (GR), which is a transcription factor, and ultimately stimulate a cascade of gene transcription changes that primarily control energy utilization; therefore, shifts in function of the HPA axis or the GR ultimately impact metabolism. Although baseline cortisol does not consistently differ among

PTSD patients (Meewisse et al., 2007; Yehuda, 2005), results indicate that PTSD is associated with a decreased cortisol response to an acute stressor (Kolassa et al., 2007). In line with this observation, enhanced glucocorticoid negative feedback on the HPA axis in PTSD is consistently reported when the system is assessed using the dexamethasone suppression test (Yehuda et al., 1995). Additionally, peripheral and central levels of corticotropin-releasing hormone (CRH), an initiating step in activation of the HPA axis, are elevated in individuals with PTSD (Baker et al., 2005; de Kloet et al., 2008). This suggests a more active HPA axis and potentially a more metabolically labile system. Furthermore, individuals with PTSD are reported to exhibit elevated GR levels (Matic et al., 2013) and enhanced glucocorticoid sensitivity (Yehuda et al., 2004) both of which would theoretically lead to enhanced GR-mediated gene transcription.

The GR is regulated by a series of co-chaperones that appear to guard against overactivation of the GR. Evidence indicates that even levels of GR's primary negative regulator are impacted in PTSD. Levels of the co-chaperone of GR, FKBP5, which inhibits GR ligand binding and nuclear translocation of GRs, are decreased in individuals with PTSD. This may contribute to the increased sensitivity of GR (Yehuda et al., 2009a) and thereby may engage transcription of other energy-related genes in PTSD patients. Rodent models of PTSD indeed have shown differential gene expression within the brain in pathways involved with obesity and metabolic syndrome [i.e. Adiponectin receptor 1 (*ADIPOR1*), dopamine 2 receptor (*DRD2*), neuropeptide Y (*NPY*)] (Muhie et al., 2015). While these findings of HPA axis dysregulation are cross-sectional in nature, prospective studies indicate that augmented baseline GR levels (van Zuiden et al., 2012), diminished FKBP5 mRNA levels (van Zuiden et al., 2012), and a blunted cortisol response to an acute stressor are all associated with increased risk for PTSD symptoms following trauma exposure, further suggesting a relationship between HPA axis dysfunction and risk for PTSD.

Many of the HPA axis modifications noted in individuals with PTSD harken back to HPA axis-centric changes documented in metabolic syndrome, including increased abdominal fat mass (being overweight or obese) (Eckel et al., 2010). Importantly, the increase in adiposity characteristic of metabolic disorders is associated with alterations in HPA axis regulation. Glucocorticoid negative feedback inhibition is diminished (Pasquali et al., 2002), cortisol response to an acute stressor is heightened (Epel et al., 2000), and morning cortisol levels are heightened (Duclos et al., 2005; Walker et al., 2000). This increased basal cortisol tone is associated with insulin resistance, glucose intolerance, and hypertriglyceridemia (Anagnostis et al., 2009). Furthermore, peripheral GR expression is increased in individuals with insulin resistance (Reynolds et al., 2002). Overall these data suggest that effects of the HPA axis and stress on metabolism act to exacerbate hyperglycemia and insulin resistance already present in metabolic disorders (Rosmond, 2005). HPA axis and metabolic alterations in both people with PTSD and people with metabolic syndrome appear to confer a state of energy availability that could promote a more efficient response to a stressor, but could also carry the adverse implications of excess energy.

It is important to note that at first glance the dysregulation of the HPA axis reported in PTSD and metabolic syndrome are opposite in nature. As described above, enhanced glucocorticoid negative feedback and diminished cortisol response to stressor exposure have

been documented in PTSD (Kolassa et al., 2007; Yehuda et al., 1995). Conversely, diminished glucocorticoid negative feedback and increased cortisol response to stressor exposure have been documented in metabolic syndrome (Epel et al., 2000; Pasquali et al., 2002). Additionally, while increased basal cortisol levels have been described in obesity and metabolic disorders (Duclos et al., 2005; Walker et al., 2000), the effects of PTSD on morning cortisol have been equivocal in nature (Meewisse et al., 2007; Yehuda, 2005). One factor that may be critical in influencing the dysregulation of the HPA axis in those with PTSD is the chronicity of PTSD and subsequent exposures to psychosocial stressors that are known to be associated with GR resistance (Gragnoli, 2014).

Furthermore, single nucleotide polymorphisms (SNPs) within the *FKBP5* gene have been shown to influence individual risk for increased GR sensitivity or GR resistance (Binder et al., 2008). More specifically, these SNPs in the *FKBP5* gene are associated with higher *FKBP5* mRNA induction upon cortisol release and increased PTSD symptom severity in those with high levels of child abuse (Binder et al., 2008). Theat-risk alleles of these *FKBP5* SNPs are associated with enhanced glucocorticoid sensitivity, whereas the other alleles of these SNPs are associated with GR resistance in individuals with PTSD (Binder et al., 2008). Thus, genetic variability in traumatized individuals with PTSD confers differential risk for GR resistance that may lead to HPA dysregulation typically seen in metabolic syndrome and obesity. Indeed, work in translational rodent models indicate that *FKBP5* mRNA expression in adipose tissue following dexamethasone administration is increased and associated with glucocorticoid-induced insulin resistance (Pereira et al., 2014). Increases in hypothalamic *FKBP5* mRNA expression have also been associated with increased body weight gain in mice (Balsevich et al., 2014).

The Sympathetic Nervous System and Metabolic Alterations in PTSD

The dysregulation of the HPA axis in PTSD is coincident with increased activity of the faster acting portion of the stress response as evidenced by increased sympathetic tone. Increased heart rate and skin conductance following an acute stressor are characteristic of individuals with PTSD (Blanchard et al., 1982; Keane et al., 1998; Orr et al., 2003; Shalev et al., 2000) and can be predictive of PTSD development in the aftermath of trauma (Shalev et al., 2000). Heart rate variability (HRV), a measure of beat-to-beat fluctuations in heart rate, is also dampened in individuals with PTSD (Shah et al., 2013), suggesting impaired autonomic regulation. Coincident with these physiological alterations in autonomic function is augmented catecholamine secretion (Southwick et al., 1999), as greater levels of circulating norepinephrine (NE) peripherally and centrally are found in individuals with PTSD (Geraciotti et al., 2001). Levels of NE in response to stressor/threat exposure are also increased in individuals with PTSD (Blanchard et al., 1991; Geraciotti et al., 2008). This increase in NE has recently been shown to be due to decreased levels of NE transporter in the locus coeruleus (Pietrzak et al., 2013). Additionally, peripheral α_2 -adrenergic receptors are attenuated in PTSD (Perry et al., 1987). Taken together, these data suggest that autonomic function is impaired in PTSD.

Metabolic syndrome and obesity are also associated with increased sympathetic activity (Canale et al., 2013; Thorp and Schlaich, 2015), including augmented muscle sympathetic

nerve activity, increased heart rate, and decreased HRV (Chintala et al., 2015; Grassi, 2007; Hsiung et al., 2015; Stuckey et al., 2015). Furthermore, urinary levels of NE and whole-body plasma levels of NE are increased in metabolic syndrome (Lee et al., 2001; Vaz et al., 1997). The effect of adiposity on sympathetic tone is driven by visceral adipose tissue, as sagittal adiposity but not subcutaneous fat is concomitant with increased heart rate and increased NE (Grassi, 2004).

The mechanisms by which adiposity is linked to augmented sympathetic tone are multifaceted. For instance, hyperinsulinemia in metabolic disorders can facilitate sympathetic tone by increasing sympathetic activity to skeletal muscle (Anderson et al., 1991; Lembo et al., 1992). Additionally, increased levels of leptin secretion due to greater adiposity in metabolic disorders indirectly affect sympathetic tone by inducing hyperinsulinemia (Thorp and Schlaich, 2015) and results in leptin resistance (Santoro et al., 2015). Hyperleptinemia also can facilitate sympathetic activity of the renal system leading to hypertension (Correia and Rahmouni, 2006). Importantly, catecholamine activity is central to the regulation of energy expenditure and body weight, primarily through the stimulatory effects of β -adrenergic receptors and inhibitory effects of α_2 -adrenergic receptors (Masuo, 2010). Polymorphisms in these β -adrenergic receptors are associated with metabolic syndrome and obesity in humans, corroborating the notion that increased adrenergic drive is pathophysiological (Masuo, 2010). Although not completely overlapping, both PTSD and metabolic syndrome are associated with disruptions of the autonomic nervous system. The interactions of these disruptions with metabolic hormones may mediate the convergence between PTSD and metabolic syndrome.

Metabolic Hormones and Metabolic Alterations in PTSD

Concurrent with changes in the HPA axis and sympathetic nervous system in individuals with PTSD are alterations in the expression and regulation of metabolic hormones. Increased leptin levels have also been described in trauma survivors with PTSD (Liao et al., 2004). Furthermore, NPY is an orexigenic peptide (Keen-Rhinehart et al., 2013) that also elicits anxiolytic responses by blocking CRH and noradrenergic activity (Britton et al., 2000; Rasmusson et al., 2000). Peripheral levels of NPY are decreased in individuals exposed to trauma (Morgan et al., 2003) and with PTSD (Rasmusson et al., 2000), while augmented levels of NPY have been associated with resilience to trauma (Morgan et al., 2002). The heightened adrenergic activity present in individuals with metabolic syndrome results in similarly increased release of NPY, as NPY is also released from catecholaminergic neurons both centrally and in the periphery and has been shown to directly control both stress- and diet-induced adipose accumulation in rodents (Zhang et al., 2014). In humans, levels of NPY are increased in obese patients (Baltazi et al., 2011; Baranowska et al., 1997), and genetic polymorphisms in the *NPY* gene are associated with increased NPY levels and influence individual risk for obesity (Yeung et al., 2011).

By definition, metabolic syndrome includes disruption to glucose metabolism and homeostasis. Similarly, insulin resistance is also present in individuals with PTSD, as PTSD is associated with a mild increase in insulin levels and increased insulin response to an oral glucose tolerance test (OGTT; (Rao et al., 2014)). Insulin and glucose responses following

acute stress exposure are also increased in men with PTSD (Nowotny et al., 2010). Furthermore, individuals with PTSD are more likely to show abdominal obesity, hyperglycemia, hypertriglyceridemia, low high-density lipoprotein (HDL)-cholesterol and hypertension (Rosenbaum et al., 2015). While the above data indicate that metabolism is disrupted in PTSD peripherally, fluorodeoxyglucose positron emission tomography (FDG-PET) studies show that central glucose metabolism is also disrupted in individuals with PTSD. Decreased activation of prefrontal regions, including cingulate gyri and the hippocampus, is present in men with chronic PTSD (Molina et al., 2010). Similarly, women with PTSD following sexual assault have lower glucose metabolic activity in the hippocampus (Kim et al., 2012), an area of the brain whose volume is decreased in PTSD (Admon et al.; Bremner et al., 2008) and has been implicated in the etiology of PTSD (Gilbertson et al., 2002). Resting glucose metabolic rate has also been shown to be increased in the amygdala of veterans with PTSD (Yehuda et al., 2009b), an area of the brain whose hyperactivity is characteristic of PTSD (Hughes and Shin, 2011).

Corresponding functional MRI studies in obese patients show increased activation of striatal regions in response to food cues (Burger and Berner, 2014). However, these studies do not examine brain areas that are implicated in the etiology of PTSD, such as the amygdala and hippocampus, as these regions are not typically of interest to studying obesity and metabolic disease. Thus, there are brain regions relevant to PTSD that have not yet been studied in the context of obesity and metabolic syndrome. In addition, there is a paucity of neuroimaging studies that characterize brain glucose metabolism in metabolic syndrome and obesity. One study suggests that decreases in brain derived neurotrophic factor (BDNF) are associated with altered brain glucose metabolism in diabetic individuals (Li et al., 2015). Moreover, alterations in brain metabolism have also been reported in metabolic syndrome, including increased myoinositol/creatine and glutamate/creatine ratios in occipitoparietal gray matter (Haley et al., 2010). This metabolic profile is a phenotype that has been linked to neuroinflammation in diabetes (Ajilore et al., 2007). Blunted neural activation in the frontal gyrus and parietal lobule during a cognitive challenge has also been described in individuals with metabolic syndrome (Hoth et al., 2011). More research is clearly necessary to understand how obesity and metabolic syndrome influence limbic and prefrontal regions typically altered in PTSD. One potential impediment to undertaking these studies is the body size limit that typically exists in utilizing MRI machines for neuroimaging data.

Overall, alterations in some of the hallmark characteristics of metabolic syndrome observed in people with PTSD further emphasize the overlap between these two disorders. However, there are some discrepancies and important caveats to consider. First, peripheral levels of NPY are decreased in individuals with PTSD (Rasmusson et al., 2000) and increased in those with obesity (Baltazi et al., 2011; Baranowska et al., 1997). This difference is likely due to sample composition, as the PTSD study was conducted only on average weight males exposed to combat-related trauma (Rasmusson et al., 2000). Studies in obesity typically compare average weight individuals to obese and overweight individuals using BMI thresholds. The study found that in males with PTSD, NPY levels were positively associated with body weight (Rasmusson et al., 2000). The finding suggests that even in a generally healthy and physically fit population increased NPY is associated with greater body weight. Other factors that contribute to the NPY level discrepancy include the chronicity of PTSD

symptoms, presence of co-morbid psychopathologies such as depression, and behavioral sources of GR resistance such as intake of high fat and high sugar diets (Scott et al., 2008), and smoking (Fu et al., 2007; Morissette et al., 2007).

Delineating the Relationships: Insight from Animal Models

As with other complex comorbid conditions, animal models play an essential role in delineating the relationship between PTSD and metabolic disorders and elucidating underlying mechanisms. Translational animal models of PTSD help assess the directionality of relationships between metabolic factors and behaviors related to PTSD. Most commonly, fear conditioning is used to assess the neurobiological and physiological systems that contribute to the manifestation of aberrant fear responses.

Fear conditioning paradigms based on Pavlovian learning have been leveraged in rodent models to study the etiology of PTSD-like phenotypes. In these paradigms, a neutral conditioned stimulus is paired with an aversive unconditioned stimulus, and after repeated exposure an association is formed so that the conditioned stimulus alone elicits the conditioned fear response (Jovanovic and Ressler, 2010). Fear conditioning in rodents results in alterations of serotonin and norepinephrine in the hippocampus and prefrontal cortex (Wilson et al., 2014a) and altered metabolism of dopamine and acetylcholine (Okada et al., 2015), both characteristics of PTSD pathophysiology in humans. Animal models have also implicated alterations in the transcriptome of the amygdala in underlying neuronal plasticity (Ponomarev et al., 2010) and changes in hippocampal plasticity via proteomic alterations (Rao-Ruiz et al., 2015). Similar to the HPA axis dysregulation in PTSD, fear conditioning in rodents has been linked to prefrontal GR activity (Reis et al., 2015) and FKBP5 expression (Chakraborty et al., 2015). This same experimental paradigm has been used to assess the effects of corticosterone on contextual fear memory formation (reviewed in (Pecoraro et al., 2006)), and the findings have been equivocal. Studies show that corticosterone administration immediately preceding fear learning both protects against (Cohen et al., 2008; Jia et al., 2015) and facilitates the formation of increased fear responses to a conditioned stimulus (Kaouane et al., 2012; Thompson et al., 2004). However, administration of hydrocortisone to humans during and immediately after trauma exposure may protect against later PTSD development by increasing serum cortisol levels, and interfering with aspects of traumatic memory function (de Quervain et al., 2000; Schelling et al., 2006).

Fear responses are, in and of themselves, normal and adaptive; therefore, contrived sensitivities must be manufactured in the laboratory in order to address the mechanisms that push the responses into the aberrant range. Frequently, environmental stressors, such as predatory stress, are used to invoke susceptibility and to further study the mechanisms of the aberrant response to fearful stimuli. One type of predatory stress model places a rodent in close proximity with a cat (Wilson et al., 2014a) or places a mouse in proximity to a rat (Burgado et al., 2014). Other predatory stress models pair the experimental animal with an aggressive conspecific (Gautam et al., 2015; Muhie et al., 2015). This exposure elicits increased anxiety-like behaviors, impaired memory recognition, and deficits in both contextual and cued fear conditioned memory (Zoladz et al., 2015). The exposure has also

been shown to increase plasma corticosterone, elevate gut-derived metabolites, and lead to hyperlipidemia as long as four weeks after the stressor exposure (Gautam et al., 2015). Exposure to predatory stress elicits an array of PTSD-like phenotypes, including increases in prefrontal and hippocampal levels of NE (Wilson et al., 2014a), increased interleukin (IL)-1 β and NALP3, and oxidative stress as measured by total reactive oxygen species (ROS) within the same regions (Wilson et al., 2013). A mouse model of aggressor exposure also elicits deficits in fear conditioning and is associated with genome-wide transcriptome alterations, including changes in expression of signals important for the regulation of the HPA axis, neurogenesis, and fear memory consolidation and extinction (Muhie et al., 2015).

Regulators of metabolism conversely modulate fear circuitry and the expression of fear. For example, fasting prior to fear conditioning impairs fear acquisition, but fasting prior to extinction improves extinction learning (Verma et al., 2015). NPY may play a critical role as it modulates both NE and CRH activity, resulting in the attenuation of anxiety-like behavior and HPA axis activity (Hastings et al., 2004; Rasmusson et al., 2000; Sah and Geraciotti, 2013). In a fear-conditioning paradigm, NPY reduces or inhibits the acquisition of contextual fear memories (Karlsson et al., 2005; Lach and de Lima, 2013) and also increases the extinction of conditioned fear in rats (Gutman et al., 2008). In addition, leptin acts to facilitate fear extinction (Wang et al., 2015), suggesting that the beneficial effect of leptin on fear expression in individuals with PTSD and metabolic disorders is diminished due to leptin resistance (Santoro et al., 2015). Contrariwise, ghrelin secretion from the stomach increases following stressor exposure via adrenergic activation of the sympathetic nervous system (Zhao et al., 2010) and enhances the formation of fear memories (Meyer et al., 2014; Spencer et al., 2015). Similar to ghrelin, insulin like growth factor II (IGF-II) enhances fear memory retention (Chen et al., 2011) and enhancement of memory formation (Stern et al., 2014). Glucocorticoid secretion serves a dual role in the face of stressor exposure. It not only influences fear memory learning, but also interferes with insulin action (Amatruda et al., 1985), leading to insulin resistance via interference of glucose transporter (GLUT 4) translocation (Garvey et al., 1989a; Garvey et al., 1989b). Although not a focus of this review, sex differences in metabolism and, in particular, sex differences in expression of glucose transporters following stress (Harrell et al., 2014; Kelly et al., 2014), may contribute to sex differences in the prevalence and incidence of PTSD (Kessler et al., 1995; Tolin and Foa, 2006).

There are limitations of validity that must be considered when translating findings from animal models of PTSD (Daskalakis et al., 2013). To have PTSD, an individual must experience or be exposed to a life-threatening event (APA, 2014). Thus, to have construct validity, an animal model must in the least utilize a life-threatening stressor. Some rodent models of PTSD, such as predator exposure and resident-intruder (social defeat) paradigms, may ascertain construct validity due to the naturalistic stressors (Burgado et al., 2014; Gautam et al., 2015; Hammels et al., 2015; Muhie et al., 2015; Wilson et al., 2014a; Zoladz et al., 2012; Zoladz et al., 2015). However, other models such as prolonged immobilization may fall short due to the artificial nature and duration of the stressor. The predictive validity of translational animal models of PTSD is further limited because only two pharmacological agents are approved for the treatment of PTSD in humans (sertraline and paroxetine), and results have been equivocal in a predator stress model (Wilson et al., 2014b) as well as in

clinical populations (Friedman et al., 2007). While all of these rodent models result in some PTSD-like phenotypes such as increased sympathetic activity and fear responses and deficits in fear extinction, it is sometimes difficult to induce phenotypes that are unique to PTSD such as dysregulated HPA function.

Furthermore, it is critical that the stressors employed in these models result in phenotype variability so that we can understand factors that explain individual vulnerability to PTSD-like phenotypes in the aftermath of stressor exposure (Daskalakis et al., 2013). One largely understudied factor that influences behavioral and physiological responses to stressor exposure in translational animal models is sex. While some models, like social defeat, inconsistently produce adverse phenotypes in females, others can be employed to study the etiology of the robust sex difference in PTSD that affect females more than males (Kessler et al., 1995; Tolin and Foa, 2006).

Inflammation as a Common Underlying Mechanism

Up to this point, we have highlighted similarities between PTSD and traditional metabolic disorders. The question then becomes, what drives these points of convergence? PTSD and metabolic disorders bear phenotypic similarities, but they are also mechanistically related. To start, one pervasive physiologic response that is capable of driving somatic and cerebral shifts in function is the inflammatory response. Heightened inflammation is highly coincident with increased sympathetic tone in obesity and metabolic syndrome. This is due to the fact that the noradrenergic system also acts to stimulate the innate immune response (Sanders, 2006), including IL-6 production (Pal et al., 2014). Additionally, levels of pro-inflammatory markers, including C-reactive protein (CRP), IL-6 and TNF α , are increased in both obesity and metabolic syndrome (Bastard et al., 2000a; Bastard et al., 2000b; Fontana et al., 2007; Gregor and Hotamisligil, 2011; Pannacciulli et al., 2001). This increase in systemic inflammation in obesity has been linked to macrophage infiltration of adipose tissue as well [reviewed in (Karalis et al., 2009)].

Exacerbated levels of IL-6 and TNF α are associated with insulin resistance and hyperglycemia in T2DM (Daniele et al., 2014). Data from *in vivo* and *in vitro* models indicate that IL-6 plays a direct role in the development of hyperinsulinemia and insulin resistance (reviewed in (Pal et al., 2014)). Recent clinical data show that increased systemic inflammation in the form of increased peripheral levels of IL-6 differentiates obese women with T2DM from obese women with normal glucose tolerance (van Beek et al., 2014).

Indeed, the neuroendocrine and autonomic phenotypes associated with PTSD described above are also coincident with increased levels of inflammation. Levels of pro-inflammatory cytokines, such as IL-6 (Maes et al., 1999), IL-1 β (Spivak et al., 1997), and IL-2 (Smith et al., 2011), are augmented in individuals with PTSD. Importantly, levels of pro-inflammatory markers are positively correlated with PTSD symptoms in traumatized individuals (von Kanel et al., 2007). Elevated levels of CRP in individuals with PTSD are associated with greater PTSD symptoms and increased odds for a PTSD diagnosis (Michopoulos et al., 2015b; Miller et al., 2001; Plantinga et al., 2013). High CRP levels are also associated with diminished inhibition of fear-potentiated startle (FPS) (Michopoulos et al., 2015b), which is

a psychophysiological biomarker of PTSD (Glover et al., 2011; Jovanovic and Ressler, 2010). Peripheral levels of nuclear factor- κ B (NF- κ B) are also increased in women with PTSD and associated with decreased sensitivity to glucocorticoid negative feedback (Pace et al., 2012). A recent systematic meta-analysis confirmed that increased inflammation is coincident with PTSD in traumatized individuals (Passos et al., 2015).

Neuroinflammation has also been studied in translational animal models and studies indicate that inflammatory processes disrupt hippocampal function via central receptors (Loddick et al., 1998; Williamson and Bilbo, 2013). Most rodent models have used lipopolysaccharide (LPS) administration to assess the effects of central and systemic inflammation on behavior and cognition. LPS administration impairs contextual fear learning in rodents, suggesting that inflammation interferes with memory consolidation (Pugh et al., 1998). More recently, studies have elucidated the mechanism by which inflammation interferes with the acquisition and extinction of fear. Specifically, LPS administration disrupts cellular processes in the hippocampus critical for memory formation (Czerniawski et al., 2015), and increases in IL-6 (Burton and Johnson, 2012) and IL-1 β (Gonzalez et al., 2013) interfere in this LPS-induced deficit in memory. Additionally, site-specific injections of both IL-6 (Hao et al., 2014) and TNF α (Jing et al., 2015) into the amygdala impair the acquisition and extinction of fear conditioning. Taken together, these data suggest that increased inflammation may serve as the biological mechanism by which metabolic alterations occur in individuals with PTSD (Figure 1). If inflammation is a driving force in the etiology and maintenance of PTSD (Felger et al., 2016), then pharmacological treatments that target inflammatory mechanisms may be effective treatment strategies for PTSD and metabolic disease intervention (Michopoulos and Jovanovic, 2015).

The use of angiotensin-converting enzyme inhibitors (ACE-I) and blockers (ARBs) for the treatment of PTSD and cardiometabolic disease may support the involvement of inflammatory mechanisms. ACE-I/ARBs are typically prescribed for the treatment of hypertension and increased sympathetic activity. These pharmacological agents not only attenuate blood pressure (Savoia and Schiffrin, 2007), but also reduce neuroinflammation (Benicky et al., 2011; Welty et al., 2015), as angiotensin-II acts as a pro-inflammatory signal to induce the release of CRP (Peng et al., 2007; Zhao et al., 2013) and IL-6 (Sano et al., 2001). Furthermore, recent findings from traumatized individuals indicate that ACE-I/ARB medication usage is associated with decreased odds for having a diagnosis of PTSD and lower levels of PTSD symptom (Khoury et al., 2012). Data from translational rodent models indicate ACE-I/ARB could act to attenuate the development and/or maintenance of PTSD by enhancing the extinction of fear memories (Marvar et al., 2014). These data suggest that use of interventions that target multiple phenotypes and underlying neurobiology may be the most efficacious in reducing the health burden of PTSD.

Of course, pharmacological interventions are not the only options available, as cognitive and behavioral therapies may also be efficacious in dampening the adverse effects of PTSD on metabolic outcomes. Community-based educational intervention in African American women, a group typically at increased risk for trauma exposure and PTSD (Gillespie et al., 2009) as well as cardiovascular disease and metabolic syndrome, was effective in reducing inflammation (CRP and TNF α) (Villablanca et al., 2015). However, it still remains to be

determined whether effective behavioral therapies for PTSD (Butler et al., 2006), including prolonged exposure (Powers et al., 2010), are also capable of reducing inflammation in traumatized individuals. Any interventions that decrease inflammation and oxidative stress could also benefit individuals with PTSD, including meditation and yoga (Black and Slavich, 2016; Pascoe and Bauer, 2015). Weight loss, decreasing adiposity via exercise, or eating diets high in omega-3 fatty acids could also mitigate PTSD symptoms. This is suggested by a study showing weight loss occurs in parallel with a decrease in BMI and PTSD symptoms in traumatized individuals (Johannessen and Berntsen, 2013).

Summary and Conclusions

In summary, the underlying alterations in sympathetic nervous system activity, neuroendocrine pathways, and metabolism described in individuals with PTSD are similar to those present in metabolic syndrome and associated phenotypes, such as obesity and diabetes (Table 1). These mutual changes in biology are concomitant with increased inflammation and suggest a common mechanism by which exposure to trauma and coincident PTSD increases risk for the development of physical diseases, including obesity and T2DM (Rosenbaum et al., 2015). Indeed, low-grade inflammation in metabolic disorders is coincident with adverse changes in behavioral and cognitive symptoms, namely mood and cognitive disruptions (Lasselin and Capuron, 2014). While the specific mechanism by which inflammation increases severity of PTSD and mood disruptions in metabolic syndrome remains uncertain, recent evidence from individuals with depression suggests that inflammation drives central alterations in corticostriatal functional connectivity that are associated with anhedonia (Felger et al., 2015).

Importantly, behavioral sources of inflammation may also contribute the increased inflammation, as those with PTSD have disrupted sleep patterns, and are more likely to engage in unhealthy behaviors such as consuming alcohol, smoking, eating poorly and a sedentary lifestyle. All of these behavioral phenotypes are associated with a pro-inflammatory state (Bryant et al., 2004; Frohlich et al., 2003; Fu et al., 2007; Jamal et al., 2014; Scott et al., 2008). Increases in adiposity due to excess energy intake and decreased energy expenditure in individuals with PTSD could also contribute to the emergence of metabolic disorders in those with PTSD via heightened secretion of pro-inflammatory cytokines and GR resistance (Karalis et al., 2009). Indeed, the epidemiologic data suggest that PTSD increases one's risk for developing metabolic disorder and cardiovascular disease (Boscarino, 2004; Rosenbaum et al., 2015). While this indicates that obesity and metabolic disorder are a consequence of behavioral phenotypes associated with PTSD in traumatized individuals, it is critical to note that PTSD in the absence of obesity is associated with increased inflammation, augmented SNS activity, and dysregulation of the HPA axis as noted in this review. However, it is not yet known whether preexisting metabolic disorder increases individual risk for developing PTSD in the aftermath of trauma. A recent study suggests that preexisting inflammation, which is a characteristic of cardio-metabolic disease, increases risk of PTSD development, as greater CRP levels pre-deployment were associated with increased risk for PTSD following deployment (Eraly et al., 2014). In active duty military personnel, increased inflammation can arise from behavioral sources (i.e. alcohol consumption) and the chronic stress associated with living with PTSD and depression (Groer

et al., 2015; Reyes-Guzman et al., 2015). This increased inflammation may be due to the rising rates of obesity in active duty military personnel (Reyes-Guzman et al., 2015), suggesting a mechanism by which inflammation may result in increased risk for PTSD development in a sample otherwise thought to be in good health.

Clearly future studies are not only necessary to elucidate the underlying etiology of metabolic changes in traumatized individuals with PTSD, but also to determine the effectiveness of therapeutic interventions aimed at attenuating the adverse mental and physical consequences of PTSD. The implications of treating PTSD as a whole-body condition are significant for treatment as doing so may elicit symptom relief in individuals suffering from these whole-body adverse outcomes. It has already been suggested that alleviating inflammation may provide benefit to individuals suffering from PTSD and metabolic disorders, and even help prevent the onset of metabolic syndrome in individuals with PTSD (Michopoulos and Jovanovic, 2015). However, empirical evidence must be generated to support the efficacy of such interventions and others designed to target other biological systems whose activity is altered in both PTSD and metabolic disorders (i.e. HPA axis, SNS). To begin to accomplish this goal, the field must recognize that chronic PTSD is both a psychiatric and metabolic disorder.

Acknowledgments

Funding Sources:

V.M. was supported by K12HD085850.

G.N.N. was partially supported by R01MH110364 and K18MH105098.

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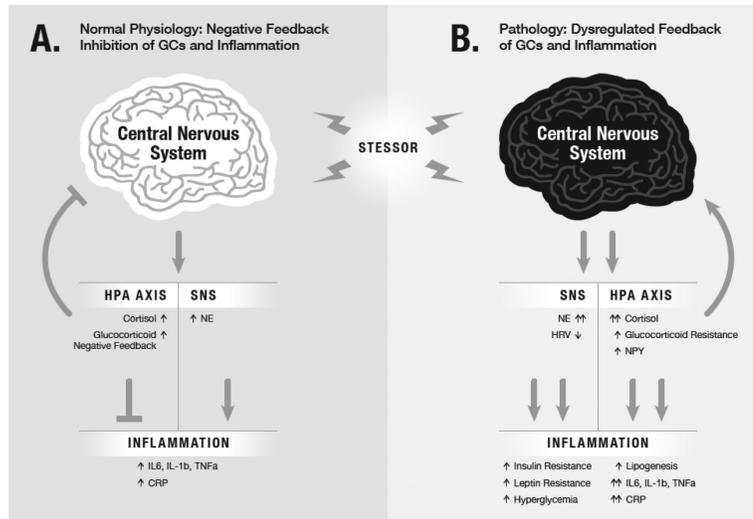


Figure 1. (A) Normal physiology: the established negative feedback inhibition of the stress axis is mediated by glucocorticoids (GCs). Exposure to a stressor activates the HPA axis and sympathetic pathways, leading to increases in GCs and pro-inflammatory cytokines (Bierhaus et al., 2003; Steptoe et al., 2007). While the sympathetic system increases cytokine release (Bierhaus et al., 2003), GCs act to inhibit subsequent GC and cytokine release in a negative feedback manner that is regulated via GC receptors (Horowitz and Zunszain, 2015; Sanders, 2006). (B) Pathology: heightened sympathetic drive (increased norepinephrine and decreased HRV) and dysregulation of the stress axis can lead to impaired GC-immune feedback such that inflammation is increased in the presence of GC resistance (Horowitz and Zunszain, 2015). The increase in GCs in this pathological state increases NPY levels, facilitates food intake and promotes lipogenesis (Michopoulos, 2016), thus further increasing inflammation that can no longer be inhibited by GC negative feedback. These downstream consequences of augmented inflammation also lead to hyperglycemia, and leptin and insulin resistance.

Table 1

Summary of biological phenotypes associated with both PTSD and Metabolic Syndrome (MetS). Arrow denotes directionality of changes associated with PTSD and MetS.

Phenotype	PTSD	MetS
HPA Axis		
Glucocorticoid receptors (GR)	↑ Peripheral GR levels (Matic et al., 2013; van Zuiden et al., 2012)	↑ Peripheral GR levels (Reynolds et al., 2002)
GR negative feedback	↑ GR negative feedback (Yehuda et al., 2004)	↓ GR negative feedback (Pasquali et al., 2002)
Cortisol levels	↓ Morning cortisol levels (Meewisse et al., 2007; Yehuda, 2005) ↓ Cortisol response to stressor (Kolassa et al., 2007)	↓ Morning cortisol levels (Duclos et al., 2005; Walker et al., 2000) ↑ Cortisol response to stressor (Epel et al., 2000)
Sympathetic Nervous System		
Sympathetic tone	↑ Heart rate and skin conductance (Blanchard et al., 1982; Keane et al., 1998; Orr et al., 2003; Shalev et al., 2000)	↑ Heart rate and sympathetic activity (Canale et al., 2013; Thorp and Schlaich, 2015)
Heart rate variability (HRV)	↓ HRV (Shah et al., 2013)	↓ HRV (Chintala et al., 2015; Stuckey et al., 2015)
Norepinephrine (NE) signaling	↑ Circulating NE peripherally and centrally (Geraciotti et al., 2001)	↑ Urinary and whole-body plasma NE (Lee et al 2001; Vaz et al., 1997)
Metabolic Characteristics		
Obesity	↑ Prevalence of abdominal obesity (Rosenbaum et al., 2015)	↑ Abdominal obesity is characteristic (Thorp and Schlaich, 2015)
Type 2 diabetes mellitus (T2DM)	↑ Risk of T2DM (Rao et al., 2014)	↑ Risk of T2DM (Thorp and Schlaich, 2015)
Insulin resistance	↑ Circulating insulin (Rao et al 2014) ↓ Insulin response to oral glucose tolerance test (Rao et al 2014)	↑ Circulating insulin (Thorp and Schlaich, 2015) ↓ Insulin response is characteristic (Thorp and Schlaich, 2015)
Glucose metabolism	↑ Prevalence of hyperglycemia (Rosenbaum et al 2015) Disrupted brain glucose metabolism (Molina et al., 2010)	↑ Prevalence of hyperglycemia (Thorp and Schlaich, 2015) Disrupted brain glucose metabolism via BDNF (Li et al., 2015)
Neuropeptide Y (NPY)	↓ NPY levels (Morgan et al., 2002; Rasmusson et al., 2000)	↑ NPY release in obese patients (Baltazi et al., 2011) NPY polymorphisms assoc. with ↑ NPY, obesity (Yeung et al., 2011)
Leptin resistance	↑ Leptin (Liao et al., 2004) Leptin facilitates fear extinction in animal models (Wang et al., 2015)	↑ Leptin (Correia and Rahmouni, 2006)
Inflammation		
CRP	↑ CRP associated with ↑ symptoms (Michopoulos et al., 2015b; Miller et al., 2001; Plantinga et al., 2013) ↑ CRP associated with ↑ fear-potentiated startle (Michopoulos et al., 2015b)	↑ CRP levels (Bastard et al., 2000a; Bastard et al., 2000b)
TNFα	↑ TNFα levels (Pace et al 2012)	↑ TNFα levels (Bastard et al., 2000b)
IL-6	↑ IL-6 levels (Maes et al., 1999) IL-6 amygdala injection ↓ acquisition, extinction of fear conditioning in animal model (Hao et al., 2014)	↑ IL-6 levels (Bastard et al., 2000a; Bastard et al., 2000b) ↑ IL-6 assoc. with insulin resistance, hyperglycemia in T2DM (Daniele et al., 2014)